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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,738	11/12/2003	John Hilfinger	TSR-10002/38	7532

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,738	HILFINGER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-16,19,20,22,24,26,27 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-16,19,20,22,24,26,27 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 8/17/07.

Claims 8-16, 19, 20, 22, 24, 26, 27, and 30 remain pending and are under consideration.

Rejections and objections not reiterated from the previous Office Action are withdrawn.

Claim Objections

Claim 8 is objected to because it is marked up to indicate an amendment, and its status is indicated as "Currently amended", but the claim is identical to the version submitted in the previous amendment entered 2/20/07. Applicant is reminded that 37 CFR 1.121 sets for the proper manner of making amendments to the claims, and requires the use of the proper status identifiers, and that the claims be marked up only to show amendments. Failure to comply can result in issuance of a Notice of Non-responsive Amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), in view of Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012).

Niedzinski taught cholic acid conjugates comprising a polyamine DNA binding domain, their use to protect DNA from degradation in the gastric system, and their use to deliver plasmids to NIH 3T3 cells in vitro. Niedzinski envisioned the use of these conjugates to deliver therapeutic nucleic acids by oral delivery to the gastrointestinal system, particularly to the enterohepatic receptors of the small intestine, which are specific for bile salts. See abstract, paragraph bridging pages 721 and 722. The cholic acid moieties were esterified through an oxygen at C3 to a DNA binding domain, or through a carboxylic acid moiety corresponding to that present on bile acids. See scheme 1, compound 5 or 6, page 722.

Niedzinski did not teach the use of cholestanol, coprostanol, glycocholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, or taurochenodeoxycholic acid. However, Niedzinski considered his conjugation technique to be applicable to a variety of bile acids (see last sentence of column 1 on page 724), and it was clear that it could be applied to either the C3 hydroxyl, so the presence of a carboxyl group was not required.

Keener taught the use of bile acids, and cholesterol derivatives generally, as hydrophobic conjugates to aid in the cellular entry of a conjugated peptide (proricin). Bile acids and cholesterol derivatives included cholic acid, coprostanol, glycocholic acid,

chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, and taurocholic acid. See column 19, lines 37-55. Thus it was clear to one of ordinary skill in the art at the time of the invention that bile acids and cholesterol derivatives were equivalent alternative hydrophobic groups in the art of conjugating hydrophobic groups to compounds intended for delivery to cells.

It would have been obvious to one of skill in the art at the time of the invention to substitute any hydrophobic bile acid or cholesterol derivative for the cholic acid of Niedzinski. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Niedzinski also did not teach peptide DNA binding domains.

Gebeyehu taught reagents and methods for intracellular delivery of nucleic acids. The reagents are cationic lipids with the general formula of ABZ, wherein A is a steroid such as cholic acid, stigmasterol, or ergosterol, B is a linker, and Z can be a nucleic acid binding domain such as a polyamine or a polycationic peptide (protamine, a histone, or a nucleic acid binding protein). See column 3, lines 50-64; column 4, lines

50-54; column 5, lines 36 and 52-58; and column 9, line 58 to column 10, line 10. Accordingly, it was clear to those of ordinary skill in the art at the time of the invention that it was routine to conjugate nucleic acid binding domains to cholesterol derivatives for nucleic acid delivery, and that acceptable nucleic acid domains included polyamines and polycationic nucleic acid binding peptides such as protamines and histones.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a nucleic acid binding peptide for the nucleic acid binding polyamine of Niedzinski because these nucleic acid binding moieties were recognized in the art as equivalents. See MPEP 2144.06.

Regarding claim 20 and the 'Y' linker peptide moiety, the first 2 or 3 amino acids of the DNA-binding peptide can be considered to be the linker peptide.

Regarding claim 30, the cited art did not explicitly teach a commercial package comprising the composition and instructions for use. However, Gebeyehu did teach kits comprising the compositions. See column 13, lines 18-24. it would have been obvious to one of ordinary skill in the art at the time of the invention to place the components of such a kit into a container. One would have been motivated to do so in order to organize the components into an easily retrievable state. One would have been motivated to include instructions because one of ordinary skill in the art appreciates that referring to instructions decreases the frequency of errors. Thus the invention as a whole was prima facie obvious.

Thus the invention as a whole was prima facie obvious.

Claims 15 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 above, and further in view of Perrie et al (J. Liposome Res. 12(1&2): 185-197, 2002).

Niedzinski, Keener, and Gebeyehu render obvious methods of delivering nucleic acids to target cells of a subject by orally administering a nucleic acid encoding a protein and a lipidic agent comprising a bile acid or cholesterol derivative conjugated to a polyionic DNA-binding peptide. The DNA/lipidic agent was also formulated with DOTAP and/or DOPE. See paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726.

These references were silent as to the secretion of the protein form the target cells, and did not exemplify a composition comprising a therapeutic compound.

Perrie taught oral intragastric delivery of cationic liposome comprising nucleic acids encoding the S (small) region of the hepatitis B surface antigen (HBsAg). DNA vaccines encoding HBsAg were formulated with cationic lipids (DOTAP) and administered orally. Immune responses against the antigen were observed. See abstract. HBsAg is a surface protein, and so is expressed and routed through the secretory pathway. Also, generation of an immune response requires presentation of the antigen on a cell surface, again requiring secretion.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the conjugate of Niedzinski as modified by Keener and Gebeyehu in

the method of Perrie. Niedzinski taught that the lipid could be substituted for, or added to, such cationic lipids as DOTAP. See paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. Thus the invention as a whole was prima facie obvious.

Claims 15 and 16 are included in this rejection because the nucleic acid of Perrie is considered to be a therapeutic product that is antibiotic in nature by virtue of its activity in inducing an immune response against hepatitis B virus.

Claims 11, 12, 15, and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Niedzinski et al (Lipids 35(7): 721-727, 2000), Keener et al (US Patent 6,627,197) and Gebeyehu et al (US Patent 6,075,012) as applied to claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 above, and further in view of Kitadai et al (Brit. J. Cancer 81(14): 647-653, 1999).

Niedzinski, Keener, and Gebeyehu render obvious methods of delivering nucleic acids to target cells of a subject by orally administering a nucleic acid encoding a protein and a lipidic agent comprising a bile acid or cholesterol derivative conjugated to

a polyionic DNA-binding peptide. The DNA/lipidic agent was also formulated with DOTAP and/or DOPE. See paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726.

These references did not teach secretion of an expressed protein, and did not exemplify a composition comprising a therapeutic compound.

Kitadai taught transfection of human gastric carcinoma cells with an expression vector encoding the secreted protein interleukin-8. Transfection was performed using the cationic lipid formulation LIPOFECTIN (DOTMA/DOPE).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the cationic lipid of Niedzinski as modified by Keener and Gebeyehu in the method of Kitadai. Niedzinski taught that the lipid could be substituted for, or added to, such cationic lipids as DOTMA and DOPE. See paragraph bridging columns 1 and 2 on page 725, and Table 2 on page 726. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Claims 15 and 16 are included in this rejection because the nucleic acid of Kitadai is considered to be a therapeutic product that is an antitumoral.

Response to Arguments

Applicant's arguments filed 8/17/07 have been fully considered but they are not persuasive.

Applicant argues that Niedzinski teaches away from the claimed invention, relying for support on page 722, first column. Applicant asserts that Niedzinski "requires" that a C(3)-functionalized cholic acid derivative. This is unpersuasive because it is false. The cholic acid moieties of Niedzinski were esterified through an oxygen at C3 to a DNA binding domain, or through a carboxylic acid moiety corresponding to that present on bile acids. See scheme 1, compound 5 or 6, page 722. Also, the statement of Niedzinski that "C(3)-functionalized cholic acid derivatives... interact with molecular receptors in the ileum, aiding delivery of molecules through the intestinal wall" is not a requirement for a C(3) modification. It is merely a statement indicating that position C(3) may be functionalized without compromising recognition by the bile salt transport system. See page 722, column 1, lines 12-17, which indicates the same of the C(24) modifications. Also note that the instant claims do not exclude C(3) modification.

Applicant also argues that Niedzinski taught that survival of DNA in the stomach or ileum fluid extracts depends on a complex of cholate amphiphiles with DOTAP and DOPE, relying on page 725, first paragraph. This is unpersuasive because the instant claims do not exclude the presence of DOTAP and/or DOPE. Furthermore, there is no logical basis for Applicant's conclusion because neither Niedzinski nor Applicant has conducted the experiment in which the DNA is complexed only with the cholic acid derivatives, and not with DOTAP/DOPE. The use of these colipids does not in any way constitute a teaching away from the independent use of a cholesterol derivative, and in any case, the claims do not exclude the use of DOTAP and/or DOPE.

Applicant argues that "Niedzinski is limited to teaching that a synthetic intermediate is suitable for the chemical synthesis of many unique derivatives of C(3)-functionalized cholic acid", and that this is not akin to suggesting the suitability of those products for a different purpose. This is immaterial. Applicant has presented no reason or evidence why one of ordinary skill would not expect the invention of Niedzinski to function with other C(3) bile acid conjugates, or for that matter with other bile acid conjugates corresponding to Niedzinski's C(24) conjugates.

Regarding Keener, Applicant argues that the bile acids of Keener are not known material based on suitability for intended use according to Niedzinski, because Niedzinski allegedly teaches a requirement for C(3) fictionalization and colipids. This is unpersuasive because, as discussed above, Niedzinski does not require C(3) modification, and there is no basis for the conclusion that Niedzinski requires colipids. Furthermore, even if Niedzinski did require C(3) modification, this has nothing to do with

whether or not the bile acids of Keener are art recognized equivalents of cholic acid. Keener taught the use of bile acids, and cholesterol derivatives generally, as hydrophobic conjugates to aid in the cellular entry of a conjugated peptide (proricin). Bile acids and cholesterol derivatives included cholic acid, coprostanol, glycocholic acid, chenodeoxycholic acid, deoxycholic acid, glycochenodeoxycholic acid, and taurocholic acid. See column 19, lines 37-55. Thus it was clear to one of ordinary skill in the art at the time of the invention that bile acids and cholesterol derivatives were equivalent alternative hydrophobic groups in the art of conjugating hydrophobic groups to compounds intended for delivery to cells. Thus one of ordinary skill could have combined the elements as set forth in the rejection by known methods and could have reasonably expected no change in their respective functions. The resulting combination would have yielded predictable results to one of ordinary skill at the time of the invention.

Regarding Gebeyehu, Applicant argues that the reference does not teach or suggest the use of any cholesterol derivative other than stigmasterol, ergosterol, or cholic acid. Gebeyehu was not relied upon to teach any derivative other than these. The cholesterol derivatives are taught by Niedzinski and Keener. Gebeyehu taught the use of nucleic acid binding domains, such as a polyamine or a polycationic peptide, in combination with a steroid such as cholic acid, stigmasterol, or ergosterol, and a linker. Clearly polyamines and cationic peptides were recognized in the art as equivalents as DNA binding domains in delivery compositions, such that it would have been obvious to substitute one for the other in the invention of Niedzinski as modified by Keener. The

fact that the delivery composition of Gebeyehu used these polyamine and peptide domains in combination with cholesterol derivatives merely makes the claimed invention that much more obvious. As discussed above, ordinary skill could have combined the elements as set forth in the rejection by known methods and could have reasonably expected no change in their respective functions. The resulting combination would have yielded predictable results to one of ordinary skill at the time of the invention. Applicant has presented no evidence to the contrary.

Applicant's remarks regarding claims 30 are unpersuasive because they do not address the basis of the rejection, i.e. it would have been obvious to one of ordinary skill in the art at the time of the invention to organize the components of the composition into a kit as taught by Gebeyehu. It would have been similarly obvious to place the kit into a container. One would have been motivated to do so in order to organize the components into an easily retrievable state. One would have been motivated to include instructions because one of ordinary skill in the art appreciates that referring to instructions decreases the frequency of errors.

Regarding Perrie, Applicant's arguments are persuasive with regard to claim 11. While the protein of Perrie is routed through the secretory pathway, it is not a secreted protein in the sense that it is released from the cell. The rejection of claim 11 over Perrie is withdrawn. The rejection of claims 15 and 16 over Perrie is maintained. Applicant's only arguments relevant to these claims rely on the Niedzinski, Keener, and Gebeyehu references, and are unpersuasive for the reasons set forth above.

Applicant's arguments regarding the Kitadai reference depend on the arguments previously set forth regarding the Niedzinski, Keener, and Gebeyehu references. Because these arguments are unpersuasive for the reasons set forth above, the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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